I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Box AF Washington, D.C. 20231 on 6-21-02.

By: Nancy Ramos Printed: NANCY RAMOS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of: Goli et al.

Title: NOVEL HUMAN CYTOKINE/STEROID RECEPTOR PROTEIN

Serial No.:	09/203,548	Filing Date:	December 01, 1998
Examiner:	Pak, M.	Group Art Unit:	1643

Box AF
Commissioner for Patents
Washington, D.C. 20231

BRIEF ON APPEAL

Sir:

Further to the Notice of Appeal filed June 11, 2001, which was received in the Patent Office June 18, 2001, the Appellants' Brief on Appeal was filed on September 24, 2001. **This paper responds to the Notice of Non-Compliance with 37 CFR 1.192(c) mailed May 21, 2002. Herewith are three copies of a new brief, with the status of the Amendment After Final updated and the discussion of the study of progesterone function removed from the Summary, as required by the Examiner. Appellants believe that this Appeal Brief is fully in compliance with 37 CFR 1.192(c).**

This is an appeal from the decision of the Examiner finally rejecting claims 18, 19, 33, and 34 of the above-identified application.

(1) REAL PARTY IN INTEREST

The above-identified application is assigned of record to Incyte Pharmaceuticals, Inc. (now Incyte Genomics, Inc.), (Reel 8678, Frame 0817) who is the real party in interest herein.

(2) RELATED APPEALS AND INTERFERENCES

Appellants, their legal representative and the assignee are not aware of any related appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the instant appeal.

(3) STATUS OF THE CLAIMS

Claims rejected:	Claims 18, 19, 33, and 34
Claims allowed:	(none)
Claims canceled:	Claims 1-17
Claims withdrawn:	Claims 20-32 and 35-42
Claims on Appeal:	Claims 18, 19, 33, and 34 (A copy of the claims on appeal, as amended, can be found in the attached Appendix).

(4) STATUS OF AMENDMENTS AFTER FINAL

The Amendment after Final Office Action under 37 C.F.R. §1.116 filed September 18, 2001, has been entered according to the Advisory Action mailed December 13, 2001.

(5) SUMMARY OF THE INVENTION

Appellants' invention is directed to polypeptide sequences comprising the human cytokine/steroid receptor protein, CYSTAR, having the amino acid sequence of SEQ ID NO:1. CYSTAR is 220 amino acids in length and has chemical and structural homology (see Figures 2A and 2B) with rat 25-Dx protein (GI 1518818; SEQ ID NO:3) and porcine steroid membrane binding protein (GI 1657409; SEQ ID NO:4) (see the specification, page 12, lines

21-25). In particular, CYSTAR shares 79% identity with rat 25-Dx protein and 93% identity with porcine steroid membrane binding protein (see the specification, page 12, lines 25-26). As illustrated by Figures. 3A and 3B, CYSTAR and rat 25-Dx protein have similar hydrophobicity plots. Rat 25-Dx protein is known to be responsive to dioxin, and expression of 25-Dx in liver was enhanced in a dose dependent fashion over a wide range of dioxin exposures. The rat 25-Dx protein was suggested to be a member of the cytokine/growth factor/prolactin receptor superfamily (see the specification, page 2, lines 4-22). CYSTAR also contains a potential transmembrane domain extending approximately from positions 18 to 43 of SEQ ID NO:1 (see the specification, page 12, lines 21-29).

Furthermore, Northern analysis shows the expression of CYSTAR in nervous, secretory, urinary, endocrine, reproductive tract and gastrointestinal tissues, including brain, spinal cord, fibroblasts, adrenal gland, liver, lung, bladder, colon, small intestine, kidney, prostate, breast, pancreas, and pituitary. Many of these tissues are associated with tumors or inflammation. Of particular note is the expression of CYSTAR in fetal and infant brain, lung, and liver/spleen, which suggests a developmental role for this molecule. (See the specification, page 13, lines 2-7.)

As such, the claimed invention has numerous practical, beneficial uses including the diagnosis and treatment of developmental disorders, toxicology testing, and drug development, none of which require detailed knowledge of how the polypeptide works. As a result of the benefits of these uses, the claimed invention already enjoys significant commercial success.

(6) THE FINAL REJECTION

Claims 18, 19, 33, and 34 stand rejected under 35 U.S.C. §§ 101 and 112, first paragraph, based on the allegation that the claimed invention lacks patentable utility. The rejection alleges in particular that since "the function of the protein is not known, the protein lacks well established utility" (Office Action mailed August 2, 2000 (Paper No. 10), page 5), and that while the specification discloses the asserted utility of using the polypeptide in treating disorders associated with aberrant cellular development, differentiation, and inflammation, there is "no nexus between the unknown properties of the polypeptide and the treatment of the disease" and thus the treatment of diseases lacks substantial utility.

Claims 18 and 33 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking adequate written description. In particular, the rejection alleges that the claimed genus of sequences having at least 95% amino acid identity to SEQ ID NO:1 is not sufficiently described as Appellants have not described the common attributes of the genus (Office Action mailed March 12, 2001 (Paper No. 13), page 6).

Claims 18 and 33 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Friedberg et al. Friedberg et al. disclose a CYP2B12 which has a 4 amino acid sequence identical to SEQ ID NO:1. Claims 18 and 33 are also rejected as being anticipated by Meyer et al. as evidenced by Falkenstein et al. Meyer et al. disclose a porcine progesterone binding protein. The Examiner alleged that this protein inherently has the sequence taught by Falkenstein et al., which has 93% amino acid sequence identity to SEQ ID NO:1. Claims 18 and 33 are also rejected as being anticipated by Jacobs et al. US 5,976,837, who disclose a porcine progesterone membrane binding protein which has 93% amino acid identity to SEQ ID NO:1. The Examiner has asserted that these references all anticipate immunological fragments of SEQ ID NO:1 (Paper No. 13, pages 8-9).

(7) ISSUES

1. Whether claims 18, 19, 33, and 34 directed to polypeptide sequences and compositions comprising the sequences meet the utility requirement of 35 U.S.C. §101.

2. Whether one of ordinary skill in the art would know how to use the claimed sequences, e.g., in toxicology testing, drug development, and the diagnosis of disease, so as to satisfy the enablement requirement of 35 U.S.C. §112, first paragraph.

3. Whether or not claims 18, 19, 33, and 34 are unpatentable under 35 U.S.C. §112, first paragraph, for reason that the invention is not described in the specification and/or particularly pointed out by the claims.

4. Whether claims 18 and 33 are anticipated under 35 U.S.C. §102 by Friedberg et al., Meyer et al. as evidenced by Falkenstein et al., or Jacobs et al.

(8) GROUPING OF THE CLAIMS

As to Issue 1

All of the claims on appeal are grouped together.

As to Issue 2

All of the claims on appeal are grouped together.

As to Issue 3

All of the claims on appeal are grouped together.

As to Issue 4

This issue pertains only to claims 18 and 33.

(9) APPELLANTS' ARGUMENTS

Claims 18, 19, 33, and 34 stand rejected under 35 U.S.C. §§ 101 and 112, first paragraph, based on the allegation that the claimed invention lacks patentable utility. The rejection alleges in particular that since "the function of the protein is not known, the protein lacks well established utility" (Office Action mailed August 2, 2000 (Paper No. 10), page 5), and that while the specification discloses the asserted utility of using the polypeptide in treating disorders associated with aberrant cellular development, differentiation, and inflammation, there is "no nexus between the unknown properties of the polypeptide and the treatment of the disease" and thus the treatment of diseases lacks substantial utility.

Appellants respectfully point out that the rejections are based solely upon the unfounded assertion that the claimed polypeptide has no known function. Appellants note that the specification discloses (see page 12) that the claimed polypeptide (CYSTAR) shares 79% amino acid identity with rat 25-Dx protein, which is known to be responsive to dioxin. Expression of 25-Dx in liver was enhanced in a dose dependent fashion over a wide range of dioxin exposures. The rat 25-Dx protein was suggested to be a member of the cytokine/growth factor/prolactin receptor superfamily (see the specification, page 2, lines 4-22). CYSTAR and rat 25-Dx protein have similar hydrophobicity plots (Figures 3A and 3B). CYSTAR also has 93% identity with porcine steroid membrane binding protein, which binds to progesterone. In addition, CYSTAR contains a potential transmembrane domain. Based on this evidence, one of skill in the art would reasonably believe that CYSTAR is a cytokine/steroid receptor protein; in particular, that it is the human membrane bound progesterone receptor.

In the face of this evidence, the Examiner has asserted that the claimed polypeptide is a receptor for which the function is not known. While acknowledging that the closest prior art (Falkenstein et al.) teaches that the protein binds progesterone, the Examiner claims that since "the protein is not the traditional progesterone steroid receptor which translocates to the nucleus which is well known", "the protein is only identified by binding characteristic [sic] which does not reveal its function." See Paper No. 10, pages 4-5. The Examiner appears to be arguing that the

claimed polypeptide (as well as the homologous protein of Falkenstein et al.) might be random proteins that happen by chance to bind progesterone. This conclusion is strongly contradicted by both the cited reference and the known art at the time. At the time of filing, it was well known in the art that certain steroid effects occurred too rapidly to be caused by nuclear translocation and transcriptional modulation. These rapid non-genomic steroid effects were understood to be due to a distinct class of membrane-bound steroid receptors, since "specific binding sites have been described in membranes for various steroids exposing pharmacological properties distinct from those of the intracellular receptors" (Falkenstein et al., page 86). See also the specification, page 3, and the reference of record (M. Wehling, (1997) "Specific, nongenomic actions of steroid hormones" Ann. Rev. Physiol. 59:365-393).

In particular, at the time of filing progesterone was known to cause nongenomic actions including effects on oocyte maturation and the spermatozoan acrosome reaction (Wehling, page 375). Membrane binding sites for progesterone had been identified on both oocyte and sperm membranes (Wehling, pages 380-381). Progesterone nongenomic action was also known to have effects on reproductive behavior, and as an anesthetic (Wehling, page 384). Thus, in contrast to the Examiner's assertions, there is a clear nexus between the function of CYSTAR and reproductive/developmental disorders. Furthermore, as discussed in Wehling (page 386), possession of steroid membrane receptors was well known to be potentially useful in allowing researchers "to devise agonists; to search for antagonists; to study proximal parts of signaling".

The Examiner has asserted that the evidence from Falkenstein et al. is insufficient to demonstrate the utility of the claimed CYSTAR polypeptide as a steroid membrane receptor, because the use of terms such as "likely" and "putative" in Falkenstein et al. allegedly indicates that further experimentation is needed (Paper No. 13, page 3).

Appellants respectfully point out that under sections 35 U.S.C. § 101 and § 112, first paragraph of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148

USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit case, this threshold is not high:

> An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

Juicy Whip Inc. v. Orange Bang Inc., 51 USPQ2d 1700 (Fed. Cir. 1999). In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991) the United States Court of Appeal for the Federal Circuit explained:

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

If persons of ordinary skill in the art would understand that there is a "well-established" utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility. Manual of Patent Examination Procedure at § 706.03(a). Only if there is no "well-established" utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464 (Fed. Cir. 1999); *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case the Patent Office bears the burden to demonstrate that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Ids.* To do so, the PTO must provide evidence or sound scientific reasoning. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would

convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

The claimed CYSTAR polypeptide has 93% identity with the porcine steroid membrane binding protein of Falkenstein et al. The statement quoted by the Examiner, that the "protein is likely to represent the first putative steroid membrane receptor" does not reflect uncertainty in the result, but rather the conventional phrasing of the scientific literature. The Examiner has not met the burden to demonstrate that a person of ordinary skill in the art would reasonably doubt the asserted utility of the claimed invention. In the previous Office Action (Paper No. 10) the Examiner asserted that the claimed polypeptide was "a receptor for which the function is not known", solely because "the protein is not the traditional progesterone steroid receptor which translocates to the nucleus which is well known" (Paper No. 10, pages 4-5). Yet the results taught by both Falkenstein et al. and Wehling clearly demonstrate the existence of a class of membrane bound steroid receptors. In addition, the conclusions of Falkenstein et al., including the line quoted by the Examiner, clearly demonstrate that those of skill in the art (Falkenstein and coauthors) reasonably believed the function of the porcine homolog of CYSTAR to be that of a membrane bound progesterone receptor.

Appellants also note that a porcine progesterone membrane binding protein having 93% amino acid sequence identity to CYSTAR was the subject of an issued United States patent, U.S. Ser. No. 5,976,837 (Jacobs et al., 1999). This issued patent serves as additional evidence that the porcine homolog of CYSTAR has patentable utility, as determined by the U.S. Patent and Trademark Office.

The Examiner does not (and cannot) dispute that the 93% homology between the porcine progesterone membrane receptor is convincing evidence that the two proteins share the same function, and thus the same utility. The Examiner must accept the applicants' demonstration that the homology between the claimed invention and the porcine membrane progesterone receptor demonstrates utility by a reasonable probability unless the Examiner can

demonstrate through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt utility. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Examiner has not provided sufficient evidence or sound scientific reasoning to the contrary. At most, the Examiner's assertions amount to the argument is that the function of CYSTAR and its porcine homolog are not known to absolute certainty. The standard applicable in this case is not, however, proof to certainty, but rather proof to reasonable probability.

The Examiner has further asserted that the teachings of Wehling do not demonstrate a clear nexus between the function of CYSTAR and reproductive/developmental disorders merely because one of the results presented in Wehling, regarding the effects of progesterone on the spermatozoan acrosome reaction, had been questioned (Paper No. 13, page 4). Appellants respectfully point out that many additional teachings of Wehling support a connection between CYSTAR function and reproductive/developmental disorders. For example, membrane binding sites for progesterone had been identified on both oocyte and sperm membranes (Wehling, pages 380-381). Progesterone nongenomic action was also known to have effects on reproductive behavior, and as an anesthetic (Wehling, page 384). Thus, in contrast to the Examiner's assertions, there is a clear nexus between the function of CYSTAR and reproductive/developmental disorders.

An additional use for CYSTAR is in expression profiling. In recent years, proteome expression profiling techniques have been developed in which the expression of numerous polypeptides is compared in two or more samples. The amino acid sequences of expressed polypeptides or polypeptide fragments are tools essential to any technology that uses proteome expression profiling. See, *e.g.*, Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, Toxicology Letters 112-13:467 (2000).

The technologies made possible by expression profiling and the DNA tools upon which they rely are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and

safety assessment. One of these techniques is toxicology testing, used in both drug development and safety assessment. Toxicology testing is now standard practice in the pharmaceutical industry. See, *e.g.*, John C. Rockett, et al., Differential gene expression in drug metabolism and toxicology: practicalities, problems, and potential, Xenobiotica 29 (7):655, 656 (1999):

> Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs.

To the same effect are several other scientific publications, including Emile F. Nuwaysir, et al., Microarrays and Toxicology: The Advent of Toxicogenomics, Molecular Genesis 24:153 (1999); Sandra Steiner and N. Leigh Anderson, *supra*. Nucleic acids useful for measuring the expression of whole classes of genes are routinely incorporated for use in toxicology testing. Nuwaysir et al. describes, for example, a Human ToxChip comprising 2089 human clones, which were selected

> ... for their well-documented involvement in basic cellular processes as well as their responses to different types of toxic insult. Included on this list are DNA replication and repair genes, apoptosis genes, and genes responsive to PAHs and dioxin-like compounds, peroxisome proliferators, estrogenic compounds, and oxidant stress. Some of the other categories of genes include transcription factors, oncogenes, tumor suppressor genes, cyclins, kinases, phosphatases, cell adhesion and motility genes, and homeobox genes. Also included in this group are 84 housekeeping genes, whose hybridization intensity is averaged and used for signal normalization of the other genes on the chip.

See also Table 1 of Nuwaysir et al. (listing additional classes of genes deemed to be of special interest in making a human toxicology microarray, including cell cycle control genes). Note in particular that the sequences of the claimed invention are included in this list of particularly important classes of genes for toxicology testing. CYSTAR is a homolog of rat 25-Dx protein which is known to be responsive to dioxin. As such, CYSTAR and the sequences encoding it are of particular use in testing potential new drugs for toxicity, since CYSTAR is already known to be responsive to one prominent toxin.

The Examiner has asserted that no nexus exists between CYSTAR and either IL-6 related diseases or toxicological testing in response to dioxin, because the homology between CYSTAR and IL-6, and CYSTAR and the dioxin responsive protein rat 25-Dx, is allegedly too low (Paper No. 13, pages 3-5). Appellants respectfully point out that the homology between CYSTAR and 25-Dx is not "much lower" than that between CYSTAR and the porcine progesterone membrane receptor. The amino acid sequence identity between CYSTAR and rat 25-Dx is 79%, and the two proteins have similar hydrophobicity plots (see the specification, page 12, lines 22-27; and Figures 3A and 3B). This homology is sufficiently high as to indicate a substantial likelihood of similar function. Moreover, since dioxin has been shown to decrease estrogen-inducible gene products, there appears to be two way cross-talk between the intracellular signaling pathways involving steroids and aromatic hydrocarbons (see the specification at, for example, page 2, lines 1-3). Thus even if CYSTAR does not itself bind dioxin, it still plays a role in mediating the responses to toxins such as dioxin, and therefore is of use in toxicological testing. Similarly, there is a high level of homology between 25-Dx, the progesterone membrane receptor, and the transmembrane domain of IL-6. In addition, dioxin exposure modulates immune and inflammatory responses (specification, page 2, lines 20-22), and loss of an estrogen source can produce an elevation of IL-6 and development of osteoclastogenic osteoporosis (specification, page 3, lines 6-18), indicating a link between steroid receptors such as CYSTAR and immune disorders.

As discussed above, the Examiner has provided no actual evidence to demonstrate that applicants' asserted utilities are not correct to a reasonable probability. At most, the Examiner's assertions amount to the argument is that the function of CYSTAR and its porcine homolog are not known to absolute certainty, but applicants need not meet such a rigorous standard of proof. Under the applicable law, once the applicant demonstrates a *prima facie* case of utility by homology, the Examiner must accept the assertion of utility to be true unless the Examiner comes forward with evidence showing a person of ordinary skill would doubt the asserted utility could be achieved by a reasonable probability. *See In re Brana*, 51 F.3d at 1566; *In re Langer*, 503

F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Examiner has not made such a showing and, as such, the Examiner's rejection should be overturned.

Based upon the above evidence, it is clear that one of skill in the art would conclude that the claimed CYSTAR polypeptides and compositions thereof would have specific, real-world utilities in the study of progesterone function through membrane-bound receptors, the treatment of reproductive and developmental disorders associated with progesterone action, and in toxicology testing. Accordingly, reversal of the utility rejections under 35 U.S.C. § 101 is requested.

Claims 18-19 and 33-34 were also rejected under 35 U.S.C. 112, first paragraph, as failing to adequately teach how to use the instant invention (Paper No. 10, page 6). The rejection set forth in the Office Action is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under § 112, first paragraph, is based on the improper allegation of lack of patentable utility under § 101, it fails for the same reasons.

Issue 3 -- The claims meet the written description requirement of 35 U.S.C. § 112, first paragraph, with respect to the recitation of polypeptides comprising a naturally occurring amino acid sequence having at least 95% sequence identity to an amino acid sequence of SEQ ID NO:1.

The requirements necessary to fulfill the written description requirement of 35 § U.S.C. 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed. Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that :

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

SEQ ID NO:1 is specifically disclosed in the application (see, for example, Figures 1 and 2). Variants of SEQ ID NO:1, in particular the preferred, more preferred, and most preferred polypeptide variants (80%, 90%, and 95% amino acid sequence similarity to SEQ ID NO:1) are described, for example, at page 13, lines 8-11. Chemical and structural features of SEQ ID NO:1 are described, for example, from page 12, line 21 through page 13, line 1. Given SEQ ID NO:1, one of ordinary skill in the art would recognize naturally-occurring variants of SEQ ID NO:1 having 95% sequence identity to SEQ ID NO:1. Accordingly, the Specification provides an adequate written description of the recited polypeptide sequences.

A. The Specification provides an adequate written description of the claimed "variants" of SEQ ID NO:1.

The Office Action has further asserted that the claims are not supported by an adequate written description because "the specification only discloses one subgenus of the human polypeptide" and "the species for the human is not known because some of the amino acids are represented by Xaa for any amino acids or unknown amino acids" (Office Action, page 6). Such a position is believed to present a misapplication of the law.

1. The present claims specifically define the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue (which are hence relevant to claims to proteins encoded by the DNA) commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

> 1. A recombinant phasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

> A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. §112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define polypeptides in terms of chemical structure, in addition to functional characteristics. For example, the "variant language" of independent claim 18 recites chemical structure to define the claimed genus:

> 18. A purified polypeptide comprising an amino acid sequence selected from the group consisting of: a) an amino acid sequence of SEQ ID NO:1, b) a naturally-occurring amino acid sequence having at least 95% sequence identity to the sequence of SEQ ID NO:1, wherein said amino acid sequence encodes a polypeptide whose expression is upregulated by dioxin...

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1. In the present case, there is no reliance merely on a description of functional characteristics of the polypeptides recited by the claims. Moreover, the functional recitations included only add to the structural characterization of the recited polypeptides. The polypeptides defined in the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims

of this type. By failing to base its written description inquiry "on whatever is now claimed," the Office Action failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*

2. The present claims do not define a genus which is "highly variant"

Furthermore, the claims at issue do not describe a genus which could be characterized as "highly variant." Available evidence illustrates that the claimed genus is of narrow scope.

In support of this assertion, the Examiner's attention is directed to the previously submitted reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <40% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., pages 6073 and 6076.) Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner et al., page 6076.)

The present application is directed, *inter alia*, to cytokine/steroid receptor proteins related to the amino acid sequence of SEQ ID NO:1. In accordance with Brenner et al, naturally occurring molecules may exist which could be characterized as cytokine/steroid receptor proteins and which have as little as 40% identity over at least 70 residues to SEQ ID NO:1. The "variant language" of the present claims recites, for example, polypeptides with "a naturally-occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1" (note that SEQ ID NO:1 has 220 amino acid residues). This variation is far less than that of all potential cytokine/steroid receptor proteins related to SEQ ID NO:1, i.e., those cytokine/steroid receptor proteins having as little as 40% identity over at least 70 residues to SEQ ID NO:1.

3. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. §112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written description inquiry in those case was based on the state of the art at essentially at the "dark ages" of recombinant DNA technology.

The present application has a priority date of March 20, 1997. Much has happened in the development of recombinant DNA technology in the 17 or more years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances one of skill in the art would recognize that, given the sequence information of SEQ ID NO:1 and SEQ ID NO:2, and the additional extensive detail provided by the subject application, the present inventors were in possession of the claimed polynucleotide variants at the time of filing of this application.

4. Summary

The Office Action failed to base its written description inquiry "on whatever is now claimed." Consequently, the Action did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1 in addition to functional limitations. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids and proteins. In addition, the genus of polypeptides defined by the present claims is adequately described, as evidenced by Brenner et al and consideration of the claims of the '740 patent involved in *Lilly*. Furthermore,

there have been remarkable advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Office Action.

The Examiner has also asserted that claim 18 limitation (b), which recites a naturally-occurring amino acid sequence having at least 95% sequence identity of SEQ ID NO:1 is new matter because the subgeneric invention of naturally occurring variants is allegedly not disclosed in the specification. Appellants note that the specification explains that the term "amino acid sequence" may refer to either naturally occurring or synthetic molecules (specification, page 5, lines 27-29), and describes probes capable of identifying naturally occurring sequences encoding CYSTAR, alleles, or related sequences (specification, page 36, lines 1-8). In addition, the specification states that "[a] most preferred CYSTAR variant is one having at least 95% amino acid sequence identity to SEQ ID NO:1." (Specification, page 13, lines 10-11.) Thus the limitation of claim 18(b) does not constitute new matter.

Accordingly, reversal of the written description rejections under 35 U.S.C. § 112, first paragraph is requested.

Issue 4 --Whether claims 18 and 33 are anticipated under 35 U.S.C. § 102 by Friedberg et al., Falkenstein et al., or Jacobs et al.

Claims 18 and 33 stand rejected under 35 U.S.C § 102(b) as allegedly anticipated by Friedberg et al. Friedberg et al. disclose a CYP2B12 which has a 4 amino acid sequence identical to SEQ ID NO:1. The Examiner contends that this is an immunologically active fragment. Claims 18 and 33 are also rejected under 35 U.S.C § 102(a) and (e) as allegedly anticipated by Falkenstein et al. and Jacobs et al, respectively. Both references disclose sequences having 93% amino acid identity to SEQ ID NO:1, which the Examiner contends would also comprise immunologically active fragments of SEQ ID NO:1.

It is well settled in patent law that a reference is anticipating under 35 U.S.C. § 102 (b) only if all elements of the claimed invention are disclosed in the reference. *In re Paulsen*, 31 USPQ2d 1671, 1673 (Fed. Cir. 1994). The claims are directed to "an immunologically active fragment of the amino acid sequence of SEQ ID NO:1 wherein said fragment generates an antibody that specifically binds to the polypeptide encoded by SEQ ID NO:1." In other words,

the claimed immunologically active fragments generate antibodies that bind specifically to SEQ ID NO:1, not to other polypeptides. The reference fragments cannot generate such antibodies, since of necessity any antibodies generated by these fragments would also bind to the reference polypeptides, which have at most 93% amino acid sequence identity to SEQ ID NO:1 (and considerably less homology in the case of the Friedberg polypeptide). Thus none of Friedberg et al, Falkenstein et al., or Jacobs et al. disclose fragments meeting the limitations of claim 18 or dependent claim 33.

Accordingly, reversal of this rejection is requested.

(10) CONCLUSION

For all the foregoing reasons and the reasons stated in Appellants' Brief On Appeal, it is submitted that the Examiner's rejections of the claims on appeal should be reversed.

Due to the urgency of this matter, including the effect of this appeal on numerous copending applications and appeals and its economic and public health implications, an expedited review of this appeal is earnestly solicited.

If the USPTO determines that any additional fees are due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

This form is enclosed in triplicate.

Respectfully submitted,

INCYTE GENOMICS, INC.

Date: June 21, 2002

Barrie Greene
Reg. No. 46,740
Direct Dial Telephone: (650) 621-7576

3160 Porter Drive
Palo Alto, California 94304
Phone: (650) 855-0555
Fax: (650) 845-4166

APPENDIX

Claims on Appeal, as Amended September 18, 2001:

18. A purified polypeptide comprising an amino acid sequence selected from the group consisting of:

a) an amino acid sequence of SEQ ID NO:1,

b) a naturally-occurring amino acid sequence having at least 95% sequence identity to the sequence of SEQ ID NO:1, wherein said amino acid sequence encodes a polypeptide whose expression is upregulated by 2,3,7,8-Tetrachlorodibenzo-p-dioxin,

c) a biologically-active fragment of the amino acid sequence of SEQ ID NO:1, wherein said fragment encodes a polypeptide whose expression is upregulated by 2,3,7,8-Tetrachlorodibenzo-p-dioxin, and

d) an immunologically active fragment of the amino acid sequence of SEQ ID NO:1 wherein said fragment generates an antibody that specifically binds to the polypeptide encoded by SEQ ID NO:1.

19. An isolated polypeptide of claim 18, having a sequence of SEQ ID NO:1.

33. A pharmaceutical composition comprising an effective amount of a polypeptide of claim 18 and a pharmaceutically acceptable excipient.

34. A pharmaceutical composition of claim 34, wherein the polypeptide has the sequence of SEQ ID NO:1.